

DISTRIBUTION AND DEPOSITION OF INHALED PARTICLES IN RESPIRATORY TRACT

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Spread of viral and bacterial diseases by way of the atmosphere requires, among other things, that infectious particles be inhaled by susceptible individuals and deposited at effective sites within the respiratory system for the initiation of disease. The critical nature of the site undoubtedly varies from one disease to another. In some cases it may be enough for particles to be deposited on surfaces of the upper respiratory tract; for others the essential point of deposition may be in the deep pulmonary spaces, which are reached only by very small particles. It is known that the depth to which inhaled particles penetrate before deposition and the percentage of particles removed from the air at various sites within the respiratory system vary with aerodynamic particle size and with breathing pattern. Hence, systematic knowledge of the respiratory retention of particulate substances, in relation to size and other factors, is necessary to a full understanding of the problems of airborne infection.

This point was given emphasis in the American Association for the Advancement of Science Symposium on Aerobiology in 1941 (4) but much of the discussion was necessarily speculative. Since then, respiratory deposition of particulate matter has been studied extensively using human subjects as well as animals. Measured values in man and animals have agreed very well with theoretical predictions based on the physical laws that govern the removal of fine particles from still and moving air. Agreement has been shown also between mineral particles and living organisms when these are described according to a common scale of aerodynamic particle size (which recognizes density and shape as well as actual dimension of the particle) and, in the case of bacterial and other hygroscopic particles, proper allowance is made for the growth of the particle by water absorption from the moist air in the respiratory system.

The findings are briefly summarized in the following paragraphs with useful distinction being made between total, upper respiratory, and

deep-lung deposition. A more extensive review of the subject recently prepared by the author (5) includes references to some major studies in this area. Excellent reviews on both the initial deposition of inhaled particles and their subsequent clearance from the lungs are found in references (2) and (6).

Total retention is essentially 100% for particles $10\ \mu$ ¹ in diameter and larger. Retention remains high down to $5\ \mu$ and then drops off (see Fig. 1), reaching a minimum of 20 to 30% at $\frac{1}{4}$ to $\frac{1}{2}\ \mu$, below which it increases again, returning to 60% or better for submicroscopic particles ($<0.1\ \mu$). The reasons for these changes with size will be made clear from more detailed examination of regional dust-trapping within the respiratory system.

The total respiratory deposition increases as breathing frequency goes down for two reasons: the transit time of air (and particles) into and out of the system is increased, thus providing a longer time for particles to settle out; and a larger fraction of inspired air reaches the lung depths (where efficiency of particle removal is highest) as the tidal volume increases with decreasing breathing frequency.

Upper respiratory retention. Total respiratory retention is the sum of the separate fractions of particles deposited at different sites within the system. As a minimum, we may distinguish between two significantly different zones of deposition: along the upper respiratory tract, down to and including the terminal bronchioles; and within the pulmonary lobule. The dust-trapping characteristics of these must be examined separately.

Upper respiratory removal is essentially 100% for particles $10\ \mu$ and larger and approximately 80% at $5\ \mu$. It drops progressively with further reduction in size and approaches zero at 1 to $2\ \mu$

¹ Particle size is expressed throughout the paper as the diameter of an aerodynamically equivalent sphere of unit density.

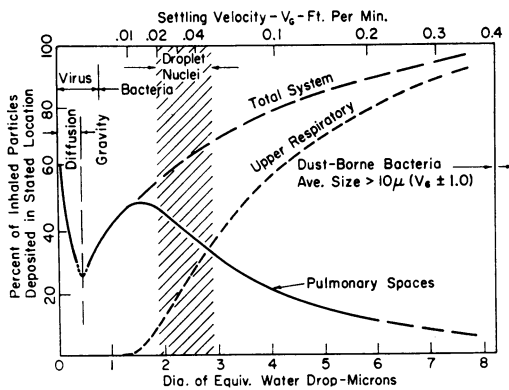


FIG. 1. Total and regional deposition of inhaled particles, in relation to the aerodynamic particle size.

as shown in Fig. 1. This minimal cut-off size goes down as breathing frequency decreases.

Penetration of particles to the pulmonary lobules. With practically complete upper respiratory deposition of $10\text{-}\mu$ particles, the probability of penetration of such large particles to the pulmonary lobules is essentially zero. Conversely, with zero trapping efficiency for $<1\text{-}$ to $2\text{-}\mu$ particles in the upper respiratory tract, the probability that smaller particles will reach the pulmonary lobules is limited only by the fraction of inspired air that goes to the lungs. Between these sizes the percentage penetration to the lobules is the product of P , per cent particles escaping upper respiratory trapping (which increases as size goes down) and V_c/V_T , the fraction of each tidal volume that reaches the lungs.

Per cent removal in lobules. Efficiency of removal of the particles which reach the pulmonary lobules is practically 100% down to 1 to 2 μ owing to the minute dimensions of these ultimate settling chambers in the lungs, but below 1 μ gravitational settling fails increasingly to remove particles. Beyond a dividing line at $\frac{1}{4}$ to $\frac{1}{2}\mu$, however, diffusion takes over as the precipitating force and efficiency of precipitation again increases, approaching 100% below 0.05 μ . Lobular efficiency will increase somewhat below 1 μ as breathing frequency goes down but there is no significant effect on retention in the submicroscopic zone where removal occurs by diffusion.

Per cent of inhaled particles deposited in the pulmonary lobules. The product of three values determines the percentage of inhaled particles

which are deposited in the pulmonary spaces: the fraction of particles which escape upper respiratory trapping; the per cent of inspired air which penetrates into the lobules; and the dust-trapping efficiency within the lobules. The curves of Fig. 1 portray the relationships for total, upper respiratory, and deep lung deposition versus particle size, at a breathing frequency of 15, all for healthy young men at rest. The curve for deposition in the lobules was derived directly from the others according to the rules given above. Summarizing from these curves:

1) The highest probability for deposition of inhaled particles in the respiratory spaces of the lungs occurs within the size range 1 to 2 μ (gravity settlement) and in the submicroscopic region below 0.2 μ (precipitation by diffusion).

2) Above 1 to 2 μ , penetration to and deposition in the lobules falls off with increasing size simply because fewer particles escape upper respiratory trapping. Above 10 μ , the probability for penetration to the lobules is essentially zero.

3) Below 1 to 2 μ , lobular deposition falls off because the efficiency of removal by gravity settlement within the lobules themselves decreases.

4) The lowest probability for deposition of inhaled particles in the respiratory system occurs at $\frac{1}{4}$ to $\frac{1}{2}\mu$, where the combined forces of precipitation by gravity and diffusion are at a minimum.

5) The probability of lobular deposition increases below $\frac{1}{4}\mu$ because the force of precipitation by diffusion increases as particle size goes down (in contrast to gravitational settlement, which decreases with size).

Site of deposition within the pulmonary lobule. Lung ventilation should be viewed as a two-stage process with actual replacement of air from breath to breath taking place to only limited depth within the lobule. According to Altshuler et al. (1), only 10 to 20% of each (resting) tidal volume replaces residual lung air. Oxygen and carbon dioxide exchange rates between the blood and this limited region of active ventilation are adequately maintained by the second stage of the ventilatory process, molecular diffusion across the static volume of alveolar air.

This concept of two-stage ventilation has interesting implications regarding the probable site of deposition of particles within the respiratory lobule. The volume of the nasal chamber and upper respiratory airways (anatomical dead-space) is about 150 ml in man. The total vol-

ume of the vestibular spaces in the pulmonary lobules (respiratory bronchioles and alveolar ducts) is approximately 700 ml. Hence, with an average tidal volume at rest of no more than 600 to 800 ml, the zone of active air replacement will scarcely extend into the alveolar recesses of the lungs. Similarly, to whatever extent particles larger than $0.4\ \mu$ do reach the pulmonary space, they will not penetrate independently into the zone of static lung air but will be deposited most probably in the respiratory bronchioles and alveolar ducts. Droplet nuclei (bacterial and virus-containing particles) are characteristically larger than $0.4\ \mu$ (see Fig. 1) and are, according to the foregoing reasoning, preferentially deposited high up in the lobule, closer to the lymphatics and to the terminal bronchioles where the mucous escalator starts clearing foreign materials out of the airways. This site of removal within the lobule may be of some importance in determining the subsequent history of the infectious particle after its initial deposition.

Quantitative significance of size differences in probability of lung deposition. The foregoing statements that $10\text{-}\mu$ particles do not reach the lungs and that $1\text{-}\mu$ particles are trapped only in the pulmonary spaces are not literally true but only relatively so. Given sensitive methods of detection and long enough exposures, we would expect to find *some* $10\text{-}\mu$ particles in the lungs and *some* $1\text{-}\mu$ particles in the nasopharyngeal chamber. A point is thus raised concerning the relative importance of the size-selective characteristics of the respiratory system against pathogenic microorganisms as compared with nonliving particulate agents. Owing to their reproductive capacities, living particles have an inherently greater potential for producing disease from the initial deposition of a few particles than could be the case for simple physical and chemical particles. This suggests that the decreasing probability of deep-lung deposition as size increases above 1 to $2\ \mu$ may not carry with it the same relative reduction in disease potential in the case of pathogenic organisms as does occur with toxic dusts. Added to this is the possibility of secondary transport of infectious particles from an initial site of deposition in the upper respiratory tract to the lungs by liquid drainage. Conceivably, these differences could be great enough largely to hide the influence of size-selection upon the relation between quantity of particles inhaled and the *effective* dose to the lungs and otherwise confuse the

picture as to the difference between the location of portal of entry of infectious particles and site of disease initiation.

Despite these precautionary statements, however, there is no lack of evidence to show that for certain diseases the influence of size is very substantial when comparison is made between fine particles such as droplet nuclei, and relatively coarse particles, comparable to dustborne bacteria. Wells and Ratcliffe (8), in an early study showed that tubercle bacilli dispersed as fine and coarse particles resulted in a 16:1 difference in the number of tubercles in the lungs of rabbits after exposure to approximately equal numbers of infectious particles in air. According to studies reported by others in this Conference (3, 7), differences of equal or greater magnitude have been obtained in comparative exposures to anthrax spores and other airborne pathogens dispersed in different sizes, within and well above the favorable size range for deep-lung deposition.

It is significant in this connection that dustborne bacteria fall characteristically in the size range 12 to $18\ \mu$ (settling velocity, $V_s = 1$ to 2 ft/min) well up in the region of upper respiratory trapping. Droplet nuclei, on the other hand, are in the optimal size range for deposition in the pulmonary spaces. Studies in hospitals, homes, and other occupied spaces have apparently given few instances where the *average* size of airborne bacteria has fallen in the size range, 3 to $12\ \mu$, between droplet nuclei and bacteria-containing dust aggregates (9). With deliberate dissemination of organisms the particles may be adjusted, of course, to any desired size; but in dealing with the natural spread of disease, it appears from the foregoing that interest centers around two categories of size, relatively fine droplet nuclei and coarse particle aggregates. These play quite dissimilar roles in determining the risk of aerial spread of different infections. In the case of droplet nuclei, in the size range 2 to $3\ \mu$ ($V_s = 0.03$ to 0.04 ft/min), Fig. 1 shows approximately equal possibilities (better than one-third) for both upper respiratory and pulmonary deposition. Accordingly, the essential site of deposition for initiation of disease does not appear to be highly critical when the infectious particles are in this size range. With dustborne particles and particles from other sources which give rise characteristically to coarse aggregations, on the other hand, it is evident that the essential site of deposition or the relative effectiveness of deposits

at various depths within the respiratory system can have great importance. If, in fact, the critical site is in the pulmonary spaces, then it will not be enough to know that the average size of the particles is above $12\ \mu$. The problem becomes statistical: Does the cloud contain *some* particles in the range of 2 to $3\ \mu$ or even between 3 and $12\ \mu$? Will the chance penetration of a few particles to the lung depths be enough to initiate disease? Is there a possibility for transport of the particles into the lungs by liquid drainage? Is it quite certain that the pulmonary spaces serve as the only portal of entry? These and other such questions have to be answered before the full dimensions of the problem of airborne infection can be delineated.

As a final comment, it is to be noted that the physical laws which largely determine the site of deposition of inhaled particles within the respiratory system also determine the relative stability of the particles in the ambient air. The risk of aerial spread of infection is certainly proportional to duration of atmospheric suspension of the infectious particles. It follows that particles dispersed in the size range of droplet nuclei are bound to be more significant contributors to airborne infection than are coarser dustborne organisms. Among the most likely candidates for aerial spread are those diseases which are uniquely dependent upon deposition of the inhaled particles in the pulmonary spaces or which are initiated by much smaller dose in the lungs than at other sites. Organisms contained in coarse aggregates of organic matter (such as dustborne bacteria) may reach susceptible individuals by way of the atmosphere and initiate disease after deposition in the upper respiratory tract. In a limited sense, the consequent disease can be thought of as airborne. But the distance of effective aerial spread is short because of high settling velocity and the brief duration of stay of the infectious particles in the air is not long enough to make

ventilation or direct air sterilization an effective measure of control. In a practical as well as a basic biophysical sense, therefore, such disease should not be classified as airborne. This point has been emphasized by Wells in his *Essay on Dustborne Infections* (9).

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